

## BED-TIME EVIDENCE

Our indoor games editor has recovered from the avalanche of letters on reading in bed (*Bandolier* 30) and from the criticism that we did not broach the incidence (or circumstance) of myocardial infarction after sex. As a tabloid we approach these topics with discretion, following in the tradition of the Parisian madame and the cardinal.

### Blanket approval

In 1966 the King's Fund produced a specification and a prototype for what became known as "the King's Fund bed". Designers at the Royal College of Art were commissioned to gather information about what was wrong with the range of beds available in the early '60s and to produce a new bed, taking into account both function and appearance.

The dramatic success of the bed and its derivatives can be seen in many countries. A new specification is part of the King's Fund centenary celebrations. The King's Fund bed needs to be systematically reviewed to take into account issues as diverse as the increasing proportion of severely disabled people managed in their own homes and changes in the staffing and running of hospitals. Readers of *Bandolier* who would like to make their opinions felt about the bed can write to the King's Fund.

### Sheets for your views

Health Technology Assessment asked us to solicit the questions which you need them to tackle (page 7). *Bandolier* knows that its readers want more evidence - get an organisation with clout to use R&D resources to provide it.

### Saturday night specials

It is infuriating (and it astonishes patients) that we don't have cast-iron evidence for all our clinical decisions. Trials take time, as do comprehensive systematic reviews. A "Saturday night special" is our term for a quick (and dirty because it does not include all the trials ever published on the topic) systematic review. The review on migraine on page 2 is a Saturday night special, and carries a health warning that it is not complete. It is unrealistic to argue that we shouldn't take a view on something until all the evidence is in. We have to do the best we can and be honest about the shortcomings.

### Night cap

Himself from indoor games stood beneath the migrating geese on Port Meadow and pondered - how do geese choose who leads the V in the flying formation?

## DRUG TREATMENTS FOR MIGRAINE

*Bandolier* has been stimulated by a number of papers on different treatments for migraine to try and put together a league table of relative effectiveness. In an ideal world this would be created from all the available evidence from systematic reviews. The problem is that the systematic reviews either have not yet been done, or anyway *Bandolier* couldn't find any.

In these circumstances the choice is either to forget it, or to press on with what evidence is available. *Bandolier*, you will not be surprised to learn, chose the latter course. So this section comes with the health warning that it is not complete - it is a "Saturday night special" review. Perhaps migraine treatment, which is now a big industry is one of those topics about which people should write to ask for a Health Technology Assessment review - see page 7.

### Sumatriptan

A review of the controlled clinical trials of sumatriptan up to 1993 was published by Peer Tfelt-Hansen from Copenhagen [1]. It contained data from an impressive number of randomised studies of sumatriptan given by subcutaneous and oral routes, and with impressive numbers of patients. Data from these papers has been extracted to calculate NNT s.

#### Subcutaneous sumatriptan

Five studies of subcutaneous sumatriptan 6 mg against placebo were highlighted in the Tfelt-Hansen review with over 2000 patients. The primary outcome measure was the effect on migraine headache. Patients rated their headache on a four-point scale (severe, moderate, mild or none) and the definition of a successful response was the decrease of a severe or moderate headache to mild or none.

The results at two hours after treatment are shown in the L'Abbé plot; the risk ratio was 2.5 (2.3 - 2.8) and the NNT was 2 (1.8 - 2.2).

This means that one of every two patients with a migraine attack treated with subcutaneous sumatriptan will have their headache cured or substantially improved, who would not have done had they been treated with placebo.

#### Oral sumatriptan

Four reports of oral sumatriptan 100 or 200 mg were highlighted in the Tfelt-Hansen review, and one other was taken from a comparison with aspirin/metoclopramide [2]. Data

from five studies and over 1100 patients were available.

Using the same outcome measures as for subcutaneous sumatriptan, the results at two hours after treatment showed a risk ratio of 2.2 (1.5 - 3.2) and an NNT of 2.6 (2.3 - 3.2).

This means that one of every four patients with a migraine attack treated with oral sumatriptan will have their headache cured or substantially improved, who would not have done had they been treated with placebo.

### Oral aspirin/metoclopramide

Two large randomised controlled trials have been reported in this last year [2,3]. One used a combination of lysine acetylsalicylate (equivalent to 900 mg of aspirin) plus 10 mg metoclopramide [2] and the other 900 mg aspirin plus 10 mg metoclopramide [3]. Both used the same outcome measure as for sumatriptan, namely headache at two hours after treatment with no or mild pain.

Combining the two studies, which had very similar results, 145/260 patients had resolution of headache with aspirin/metoclopramide compared with 61 of 255 patients with placebo. The risk ratio was 2.3 (1.8 - 3.0) and the NNT was 3.1 (2.5 - 4.2).

This means that one of every three patients with a migraine attack treated with oral aspirin/metoclopramide will have their headache cured or substantially improved, who would not have done had they been treated with placebo.

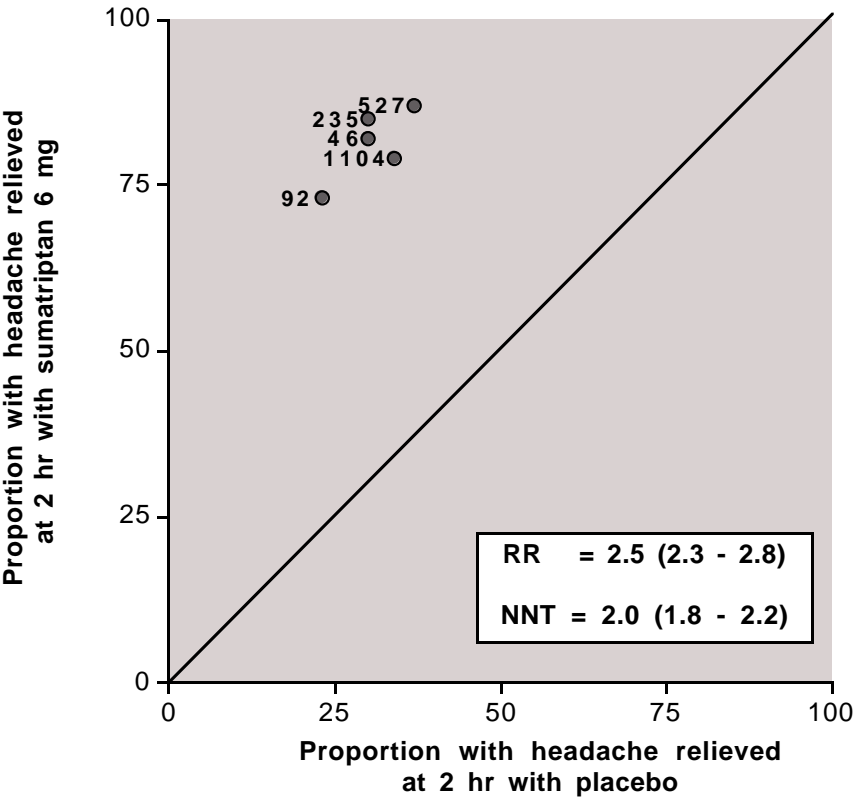
### Intranasal lignocaine

A trial reported in JAMA in July 1996 demonstrated effectiveness for intranasal lignocaine in migraine [4]. The theoretical site of action is the sphenopalatine ganglion which lies a few millimetres below the nasal mucosa.

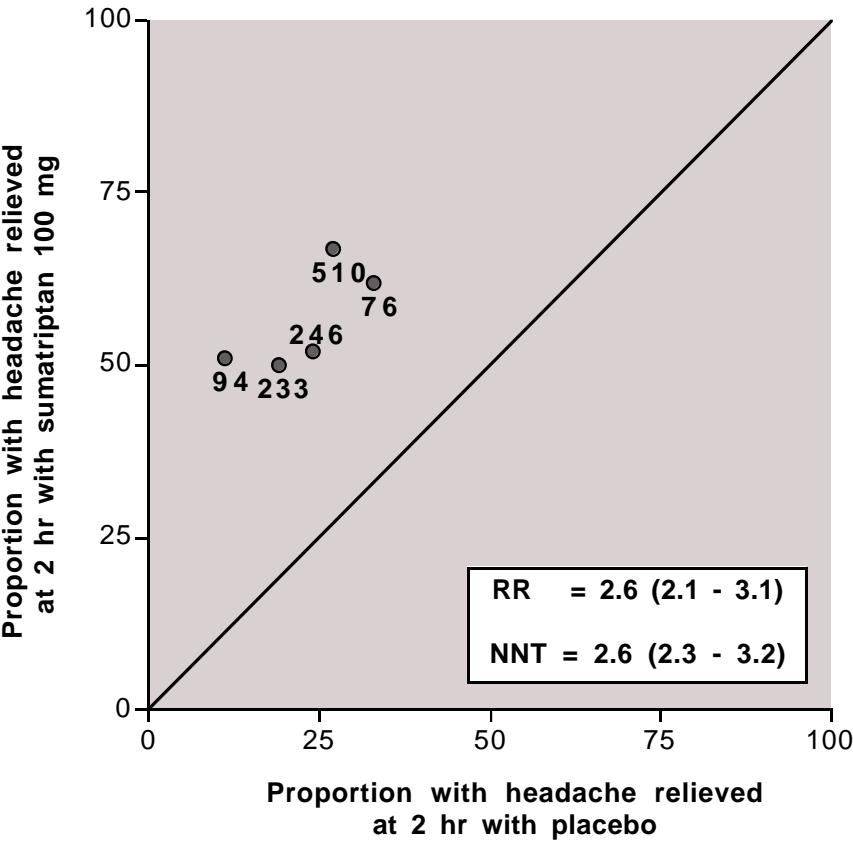
In this solitary randomised trial patients received either a 4% solution of lignocaine or normal saline. Patients lay supine with the head extended and rotated towards the side of the headache, and 0.5 mL of solution was dripped into a nostril over 30 seconds. The outcome measure was the reduction of headache pain to none or mild, and at least 50% reduction in initial pain intensity.

By 15 minutes after the intranasal application, 29 of 53 patients given intranasal lignocaine had pain relief, compared with 6 of 28 given saline. The risk ratio was 2.6 (1.2 - 5.4) and the NNT 3.0 (1.9 - 7.7).

### Randomised trials of subcutaneous sumatriptan versus placebo: headache relieved at 2 hours with numbers of patients in active and placebo groups



### Randomised trials of oral sumatriptan versus placebo: headache relieved at 2 hours with numbers of patients in active and placebo groups



This means that one of every three patients with a migraine attack treated with intranasal lignocaine will have their headache cured or substantially improved, who would not have done had they been treated with placebo.

## Anticonvulsant prophylaxis

A systematic review of anticonvulsants in chronic pain [5] identified three randomised trials where prophylactic use of anticonvulsants (carbamazepine, clonazepam or valproate) was compared with placebo in migraine. Two studies had dichotomous outcomes (improvement in number of migraine attacks), and 63 of 74 patients benefited with anticonvulsants compared with 17 of 77 given placebo.

The risk ratio was 3.9 (2.5 - 5.9) and the NNT was 1.6 (1.3 - 2.0).

This means that one of two patients suffering from migraine and treated prophylactically with anticonvulsants will have their headache frequency reduced, who would not have done had they been treated with placebo.

## Relative effectiveness

The relative effectiveness of these interventions can be seen in the figure below. Lower NNTs means greater treatment-specific effectiveness.

Intranasal lignocaine should probably be regarded as an experimental (and inconvenient) treatment. Prophylactic

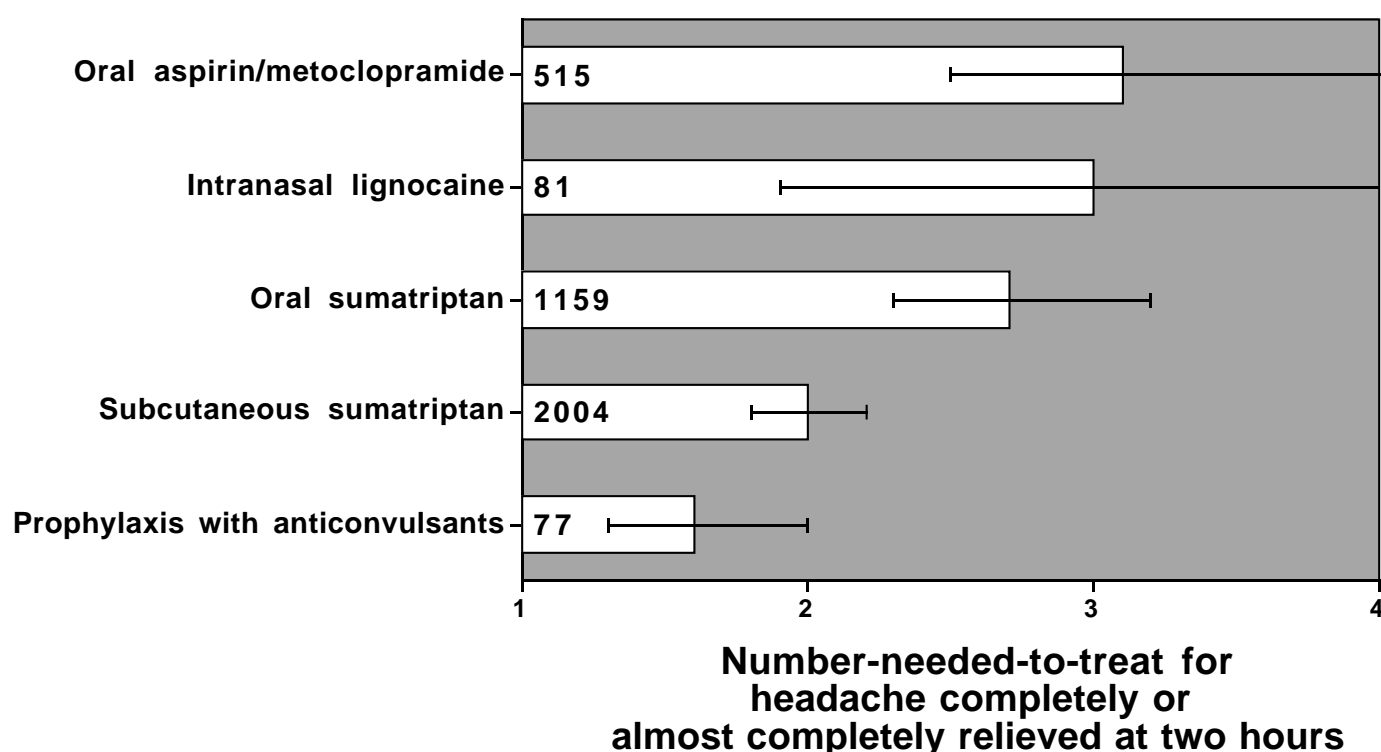
anticonvulsants carry minor adverse effects as frequently as effectiveness, and with only three small randomised trials their use can also be regarded as experimental; no anticonvulsant is licensed for use in migraine prophylaxis.

While subcutaneous sumatriptan is clearly the most effective of the other three treatments, it is also the most expensive at about £20 per treatment. Oral sumatriptan is less effective, and while cheaper than subcutaneous is quite expensive at about £8 per treatment. Oral aspirin/metoclopramide is about effective as oral sumatriptan, and the cheapest at about £0.33 per treatment.

### References:

- 1 P Tfelt-Hansen. Sumatriptan for the treatment of migraine attacks - a review of controlled clinical trials. *Cephalalgia* 1993 13: 238-44.
- 2 P Tfelt-Hansen, P Henry, L Mulder et al. The effectiveness of combined oral lysine acetylsalicylate and metoclopramide compared with oral sumatriptan for migraine. *Lancet* 1995 346: 923-6.
- 3 P Henry, O Hiesse-Provost, A Dillenschneider, H Ganry, I Insuasty. Efficacité et tolérance de l'association effervescente aspirine - metoclopramide dans le traitement de la crise de migraine sans aura. *La Presse Médicale* 1995 24: 254-8.
- 4 M Maizels, B Scott, W Cohen, W Chen. Intranasal lidocaine for treatment of migraine. *Journal of the American Medical Association* 1996 276: 319-21.
- 5 H McQuay, D Carroll, A Jadad, P Wiffen, A Moore. Anticonvulsant drugs for management of pain: a systematic review. *British Medical Journal* 1995 311: 1047-52.

**Relative effectiveness of treatments for migraine compared with placebo with total numbers of patients in active and placebo groups**



# RISK FACTORS FOR SUBARACHNOID HAEMORRHAGE

The process of systematic review is being applied in an ever-increasing number of fields. *Bandolier* was impressed by a systematic review of the risk factors for subarachnoid haemorrhage (SAH) from Utrecht [1].

## Methods

Searches were done to find reports with the following criteria:-

- SAH had to be recognised and analysed as a separate entity and not be included with a haemorrhagic stroke group.
- Studies had to present crude data that could be recalculated in the analysis.
- Case and control subjects had to be comparable, without additional criteria for controls.
- For case-control studies the diagnosis of SAH had to be confirmed in over 70% of the cases by the presence of sub-arachnoid blood on CT or by demonstration of an aneurysm during angiography or autopsy
- For the longitudinal studies the diagnosis had to be based on a review of the medical records and not only on ICD codes.

Data were analysed on the basis of the following risk factors:-

- Alcohol consumption (none, <150 g/week, >150 g/week).
- Smoking (never smokers, former smokers, current smokers).
- Hypertension
- Hypercholesterolaemia.
- Oral contraceptive use
- Hormone replacement use

## Results

There were nine longitudinal studies and 11 case-control studies which met the inclusion criteria. The figure shows results from more than one study.

Consistent increased risk was found for smoking, hypertension and alcohol intake of more than 150 grams/week (an average drink contains 12 grams of alcohol). Oral contraceptive use, hormone replacement therapy, and hypercholesterolaemia were not associated with an increased risk.

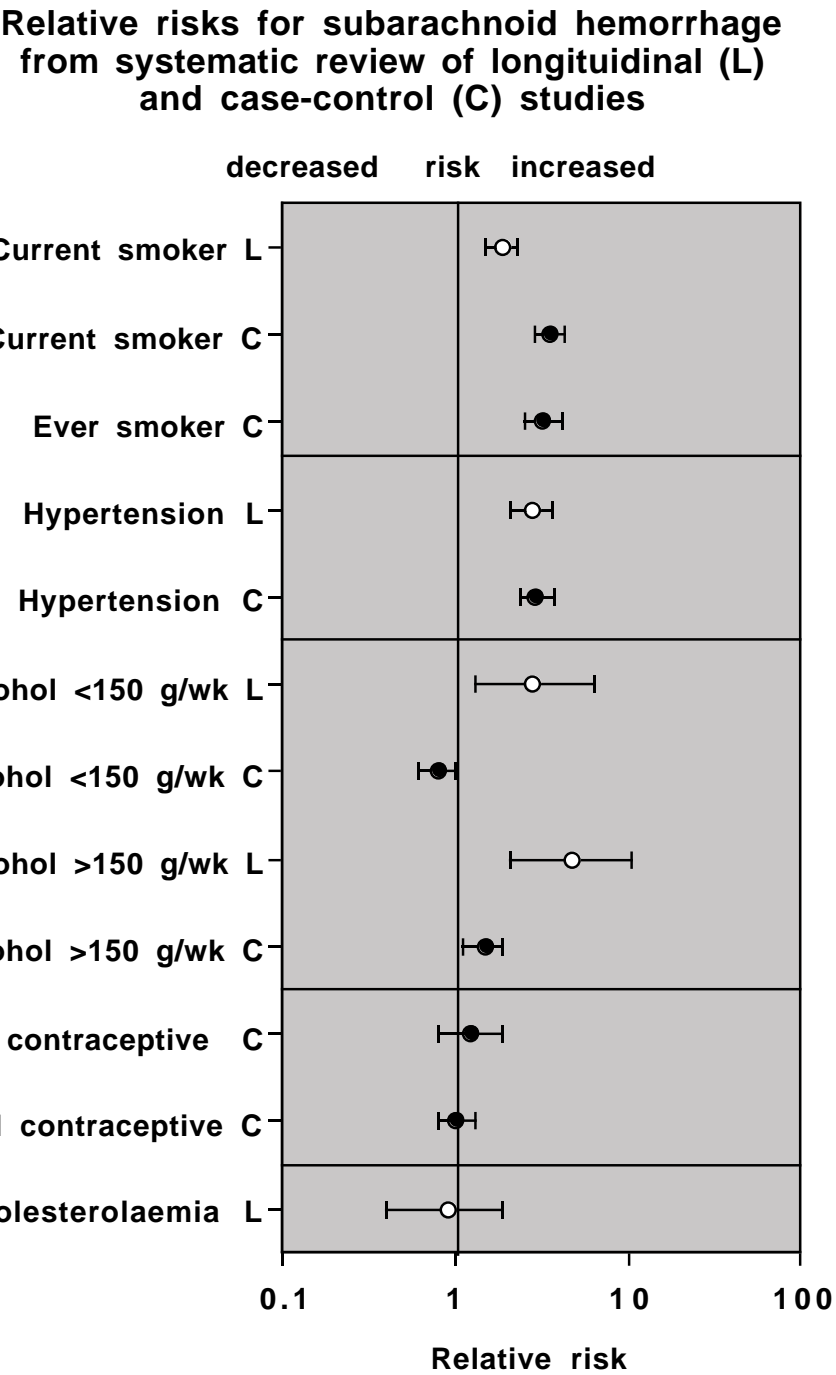
One study showed a possible protective effect of physical exercise with a relative risk of 0.5 (0.3 - 1.0), though the 95% confidence intervals just included 1.

## Comment

The incidence of SAH is low, but about half of all patients who suffer SAH die due to the initial impact of the haemorrhage. Reducing deaths from SAH depends on reducing the risk for SAH in the population as a whole: those risks are the same as those for coronary artery disease, smoking, hypertension, lack of exercise and drinking too much.

Reference:

- LL Teunissen, GJE Rinkel, AAlgra, J van Gijn. Risk factors for subarachnoid hemorrhage: a systematic review. *Stroke* 1996 27: 544-9.



## MINDSTRETCHER

### IUD USE AND THE RISK OF ECTOPIC PREGNANCY

The trouble is that it isn't as simple as the title suggests. *Bandolier* had a real problem getting its mind around a detailed and worthy systematic review and meta-analysis of case-control studies on this topic from Brussels [1].

It starts off in the usual way - searching for papers which examined ectopic pregnancy and IUD use (though only in English, French and Chinese). Finding 16 studies follows, and the data extraction, quality scoring and pooling of odds ratios is all pretty standard stuff. It is the results and what they mean that stretched *Bandolier's* mind on this occasion.

#### Results

There is a fair amount of statistical to-ing and fro-ing in the paper, but the main results are not contentious, and are shown in the figure in their most conservative form. For current IUD use, women with an ectopic pregnancy are six times more likely to have an IUD when compared with women in the second or third trimesters of a pregnancy. But women with an ectopic pregnancy are no more likely to have an IUD than women who are not pregnant.

#### Framing

The issue is one of framing, or what question is being asked. That means that it is the choice of controls that makes the result. In an ideal situation, controls would be chosen from the same population as the cases, but that is not always easy, as the case of ectopic pregnancy indicates.

Women who have an ectopic pregnancy may:

- 1 Not want to get pregnant.
- 2 Want to get pregnant.
- 3 Not be worried either way

The trouble is that we don't know what particular mix we have in any one study.

If we want controls for group 1, then we choose women from the non-pregnant age-matched population. These women probably would have the same likelihood of having an IUD as our cases - which is just the result we find. What this tells us is that women with an IUD in situ do not have an increased risk of having an ectopic pregnancy.

If we want controls for group 2, then we choose women who are pregnant (on the grounds that most of them would want to get pregnant). But these women would be less likely than all women of the same age to be using contraception, and hence IUDs. So finding a higher rate of IUD use in women with ectopic pregnancy compared with pregnant controls is the expected result. What this tells us is that a pregnancy with an IUD in situ is more often an ectopic one than a pregnancy with no IUD in place.

The past IUD results tell us that former IUD use can mildly elevate the risk of ectopic pregnancy.

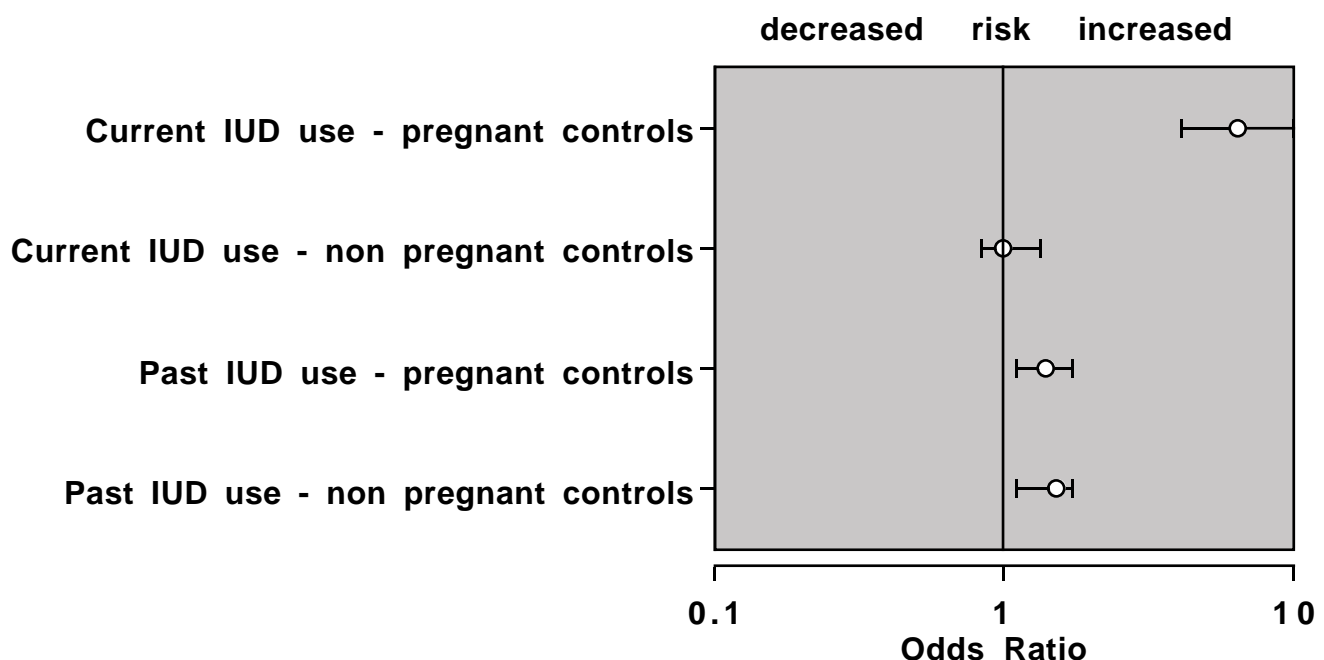
#### Comment

This is a useful paper, not only on the risks of ectopic pregnancy, but also on the limitations and difficulty with case-control studies. You may need to read it more than once.

Reference:

- 1 X Xiong, P Buekens, E Wollast. IUD use and the risk of ectopic pregnancy: a meta-analysis of case-control studies. *Contraception* 1995 52: 23-34.

### Case-control studies of IUD use and the risk of ectopic pregnancy



# ANTI-OESTROGEN THERAPY DOESN'T WORK IN MALE INFERTILITY

Anti-oestrogen therapy has been used for treatment of infertility in men with oligospermia with variable results. A systematic review from McMaster University in Ontario tell us that it doesn't work [1].

## Methods

Reports were sought on male infertility or oligospermia treated with clomiphene, tamoxifen or other anti-oestrogens. Studies included needed to fulfil the criteria of:

- Couples with at least 1 year of infertility
- Male partner oligospermia with normal gonadotrophins
- Anti-oestrogen treatment for the male partner
- Control of placebo, no treatment or equivalent
- Pregnancy rate as an outcome measure
- Randomised double blind description

## Results

Nine studies fulfilled the inclusion criteria. Six used clomiphene and three tamoxifen, and the duration was from six to 14 months.

The figure shows that most studies had pregnancy rates no higher for treated than untreated groups, and the overall odds ratio of 1.6 had a 95% confidence interval that included 1. There was no difference between clomiphene and tamoxifen.

## Quality effect

The reviewers examined the effect of trial quality using a validated quality scale. The scale has a range of 1 - 5 for included studies.

Of the nine studies, two had scores of 3 or more indicating adequate randomisation and blinding. For these two the odds ratio was 0.5 (0.2 - 1.5), showing no effect of treatment.

Seven studies had a quality score of 2 or less, showing inadequate or unclear randomisation and blinding. For these studies the odds ratio was 2.6 (1.2 - 5.2), suggesting a positive effect of treatment.

## Comment

*Bandolier* has reported previously the observation that inadequate randomisation and blinding can result in over-estimation of the size of a treatment effect. This study demonstrates yet again the importance of looking at the methodological quality of reports, especially as here, when the size of an effect is not large.

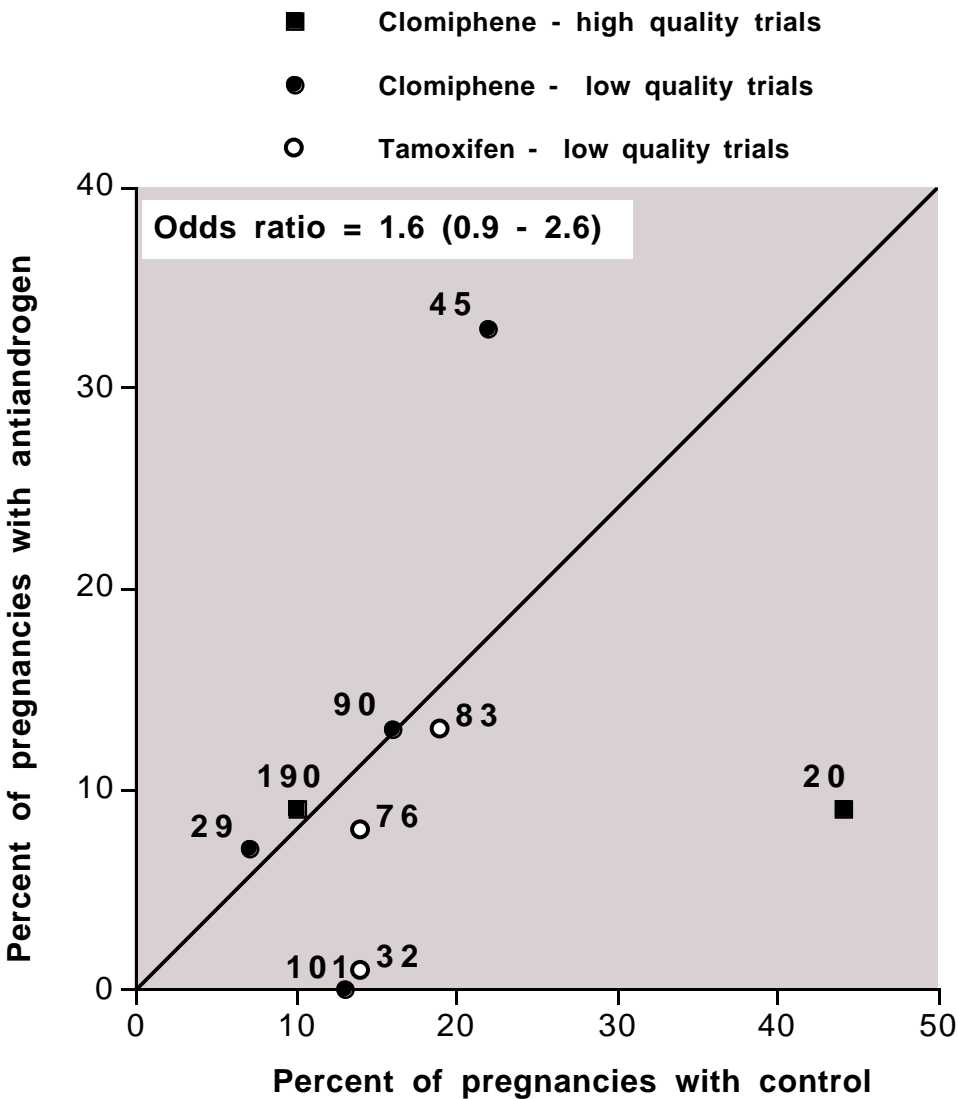
While the overall result is negative, it may have been possible for a few more studies of poor methodological quality to have tipped the balance to suggest a positive effect that just wasn't there. It's all a question of keeping up the standards.

The bottom line, though, is that this is a treatment we can forget about.

Reference:

- 1 KS Khan, S Daya, AR Jadad. The importance of quality of primary studies in producing unbiased systematic reviews. Archives of Internal medicine 1996 156: 661-6.

## Anti-oestrogen therapy in subfertile men treated with:



# CONSULTATION TO IDENTIFY NHS R&D PRIORITIES

## The National Health Technology Assessment Programme

Few common procedures and interventions used in the NHS have been evaluated rigorously, nor have the majority of the increasing number of new treatments and interventions. We often do not know which are the most effective or cost-effective interventions for use in the NHS, and in what circumstances they can be used to best effect.

The National HTA programme is the centrepiece of NHS R&D strategy. Its aim is to commission research to reduce uncertainties on the effectiveness and cost-effectiveness of health technologies.

Health *technologies* are defined very broadly as:

- all methods used by health professionals to promote health, prevent and treat disease, and improve rehabilitation and long term care

Health *technology assessment* is defined more tightly to mean:

- evaluation of effectiveness or cost-effectiveness using outcomes relevant to patients. Both systematic reviews and primary research are funded by the programme.

The HTA programme is now starting its review of priorities for 1997. The NHS Health Technology Assessment programme is asking for suggestions for consideration by the programme's six advisory panels (Acute Sector, Diagnostics and Imaging, Methodology Primary and Community Care, Pharmaceutical and Population Screening). Suggestions do not have to be precise but HTA is asking for some supporting points through the form below. Please feel free to complete as many forms as you wish. Forms should be returned by 3rd January 1997 to Deborah Anthony at the address below.

### Health technology for assessment:

Patient group and setting (e.g. hospital, GP surgery, community etc.):
Reason?
How well has the technology been researched so far?
Type of research required? i.e. primary or secondary research, if possible including any study design details
Your name, position and address:
Suggested expert? If possible please give address

Please return this form to: Deborah Anthony Researcher, National Co-ordinating Centre for HTA (NCCHTA), Wessex Institute for Health Research and Development, Dawn House Winchester. Or fax: 01962 877425 or e-mail: [hta@wiphm.soton.ac.uk](mailto:hta@wiphm.soton.ac.uk)

# BENZODIAZEPINES IN THE ELDERLY

*Bandolier* occasionally comes across an excellent review which is very difficult to précis. One such is a review of the benefits and risk of the use of benzodiazepines for insomnia for community-dwelling elderly from Ronald Grad in Montreal [1]. The highlights of the review are given below but the full flavour of the evidence can only be conveyed by reading the paper. So our best advice is that if this is an issue of interest to you, it is worth requesting from your local library

## Benefits

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There were 10 studies which met inclusion criteria for assessing benefit, none of which addressed the long-term effectiveness of benzodiazepines for treatment of sleep disorders in the elderly.

In sleep-laboratory settings, triazolam 0.125 mg, flurazepam 15 mg and estazolam 1 mg made people fall asleep about 30 minutes sooner than did placebo. They also increased total sleep time by 50 - 80 minutes for the first 2-3 nights.

## Risk

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Ten observational studies examined the relationship between benzodiazepines and adverse events like falls, car crashes and hip fracture. The larger studies (but generally not the smaller ones) showed that long-acting benzodiazepines (though not short acting benzodiazepines or sedative hypnotic drugs) were associated with an increased risk of hip fracture.

The overall risk was significant, but weak in magnitude - risk estimate 1.6 to 1.8. The public health perspective is that despite the small magnitude of the risk, the large number of elderly people given long-acting benzodiazepines for insomnia may be a cause of a significant minority of hip fractures.

## Comment

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The strength of the evidence here is weak. Grad makes enough of a point to consider avoiding the prescription of long-acting benzodiazepines for insomnia in the elderly

Reference:

- 1 RM Grad. Benzodiazepines for insomnia in community-dwelling elderly: a review of benefit and risk. *Journal of Family Practice* 1995 41: 473-81.

